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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/876,187	06/05/2001	Stuart A. Lipton	P-LJ 4714	5845

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/876,187	LIPTON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.-J

DETAILED ACTION

The response filed May 31, 2005 (referred to herein as "the response") has been entered.

Claims 1-20 and 58 remain pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 and 58 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-6 of the Office Action mailed 6/16/04 and on pages 2-12 of the Office Action mailed 11/29/04, and for further reasons as discussed herein, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

The following factors have been considered.

Nature of the invention and scope of the claims. The claims are directed to a method of differentiating progenitor cells, particularly embryonic stem cells and hematopoietic stem cells. The claims encompass *in vivo* and *in vitro* applications of the method. The claims cover a wide variety of

different types of stem cells and progenitor cells that could be used as the starting material. The progenitor cell may be in culture or may be an endogenous cell residing *in vivo*. The specification asserts that the cell compositions developed from the claimed method are useful in therapeutic transplantation. Thus, the sole asserted utility for the claimed invention is to produce a therapeutic effect. The claims are broad in scope and cover the use of any differentiating agent in combination with any progenitor cell, as well as a wide variety of MEF2 polypeptides encoded by the nucleic acid. Consequently, the method covers the production of a very large variety of heterogeneous cell compositions that comprise protected neuronal cells.

Amount of direction or guidance presented and the presence or absence of working examples. The examples of the specification are limited to producing a cell composition from a mouse embryonal carcinoma cell line (P19 cells) transfected with an MEF2 nucleic acid molecule or mouse ES cell line (D3 cells) transfected with an MEF2 nucleic acid molecule. Cells expressing MEF2C exhibited a bipolar cell phenotype that expresses both neuronal (neurofilament) and myogenic (myosin heavy chain) markers (specification at page 68, paragraph 2). All experiments were in vitro assays. The specification does not provide examples of *in vivo* differentiation or *in vivo* transfection of progenitor cells. The specification teaches that the cell compositions produced from the claimed method can be used to treat a wide variety of neurodegenerative diseases, including Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Alzheimer's disease and other forms of dementia, multiple sclerosis, epilepsy, and pain (pages 1-3). With regard to the use of the cell compositions produced, i.e. for treatment of a neurodegenerative disease, the specification provides only general guidance rather than specific guidance. With regard to *in vivo* uses of the method to produce a treatment effect, the specification provides little to no guidance. The specification does not assert a utility for the *in vivo* application of the method in the absence of a treatment effect. The specification does not offer specific guidance as to how the cell compositions produced can be used therapeutically for any given disorder.

No working examples demonstrate a therapeutic effect upon transplantation of the claimed composition. Methods of treating neurodegenerative disorders by cell therapy or *in vivo* gene therapy are in their infancy. Therefore, considerable guidance is needed.

State of the prior art and predictability of the art. The specification fails to provide an enabling disclosure for the therapeutic use of the cell compositions produced from the claimed method. Thus, the specification fails to teach how to use the claimed invention for the only asserted utility. At the time the invention was made, successful implementation of cell therapy and gene therapy protocols was not routinely achievable by those skilled in the art.

Rossi and Cattaneo (2002) acknowledge that "despite intense research activities and media attention, stem cell therapy for neurological disorders is still a distant goal" (abstract). The reference emphasizes the need for homogeneous populations of neural stem cells and the further need to understand the mechanisms required for "their proper integration into the injured brain" (abstract). The authors point out that "the functional integration of donor cells remains a highly demanding task that requires a profound understanding and control of the biological properties of both donor cells and the host environment" (page 401, column 2, paragraph 2, last sentence).

Cao et al. (2002) acknowledge the potential for the use of stem cells in therapeutic transplantation and for *in vivo* manipulation of endogenous precursors, but emphasize that "this at present is challenging and so far has been unsuccessful" (abstract and page 507, column 2, paragraph 2). The authors further point out that "[u]nderstanding mechanisms of NSC differentiation in the context of the injured CNS will be critical to achieving these therapeutic strategies" (abstract and page 507, column 2, paragraph 2).

Even under the best conditions, cell therapy in the central nervous system is highly unpredictable. For example, Milward et al. (1997) demonstrates that transplantation of neural stem cells (NSCs) to the CNS does not produce a therapeutic effect in a diseased animal. Milward et al. describes the transplantation of canine CNS NSCs into both rat and a shaking pup myelin mutant dog. In the rat, this

resulted in the production of myelin by graft-derived cells. The authors report that the grafted cells integrated normally into the adult shaking pup cytoarchitecture. Yet despite all this, the clinical deficit of these animals was not ameliorated. Thus, it is clear that the production of myelin *in vivo* and normal integration of cells is not predictive of a therapeutic outcome. Given the unpredictability in the art of therapeutic transplantation, the development of therapeutic protocols requires substantial experimentation.

Mehler et al. (1999) disclose that many studies have suggested that the normal adult brain may lack the appropriate environmental signals to allow neural progenitors to realize their broad lineage potential. Specific neuropathologic conditions may alter the normal balance of regional environmental signals, for example by releasing proinflammatory and other modulatory cytokines. The presence of these inappropriate cellular cues may predispose residual neural populations to undergo apoptosis. The authors state that "[t]his suggests that it may be necessary to promote lineage commitment of progenitor cells *in vitro* prior to transplantation into a damaged brain" (p. 782, column 1, paragraph 1).

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

In view of the quantity of experimentation necessary to determine appropriate parameters for using the resulting cell compositions to achieve a therapeutic outcome, and given the lack of applicable working examples directed to therapeutic transplantation, the limited guidance in the specification with regard to transplantation protocols and their applicability to pathologic conditions, the broad scope of the claims with regard to the wide variety of progenitor cells that may be used and the wide variety of cell compositions that may be developed from the claimed method, and further given the unpredictability in the art of therapeutic transplantation, undue experimentation would have been required for one skilled in

the art to practice the claimed methods to make useful cell compositions and use the claimed method in vivo to achieve a therapeutic effect.

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the wide variety of progenitor cell types that could be used, the unpredictability for achieving a therapeutic effect upon the transplantation of the resulting cell compositions, and the unpredictability for carrying out the claimed method *in vivo*, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention in a human patient for therapeutic benefit.

Even as late as 2001, the art acknowledged that gene transfer into human hematopoietic stem cells was problematic (Hanazono et al., 2001). The claimed invention must be enabled at the time of filing. However, the priority date of this application is June 5, 2000. Thus, the instant specification must provide an enabling disclosure for the claimed invention as of this priority date.

The specification fails to provide an enabling disclosure for the genetic modification of human ES cells. The recent literature addresses the difficulties encountered in attempting to transfect human ES cells. Zwaka et al. (2003) points out that there are significant differences between mouse and human ES cells and that "[h]igh, stable transfection efficiencies in human ES cells have been difficult to achieve, and, in particular, electroporation protocols established for mouse ES cells work poorly in human ES cells" (abstract). Thus, it is clear that the behavior of mouse ES cells is not predictive of human ES cells. In April 2001, Eiges et al. compared the efficiency of several different transfection protocols for human ES cells. The reference demonstrates use of the transfection protocol of ExGen 500 to transfect human ES cells. However, the instant specification teaches the use of adenovirus transduction for the genetic modification of human ES cells. Example 6 of the specification describes the transfection of human ES cells with an adenovirus carrying the β-galactosidase reporter gene. Although the disclosure states that

"[s]taining for expression of the β-galactosidase marker gene was performed," no results are provided with regard to the detection of β-galactosidase-expressing cells. Thus, at the time of filing, methods for successfully transfecting human ES cells were not known. The teachings of Eiges et al. (2001) would not have been available to the skilled artisan as of the filing date of this application which is July 27, 2000.

Regarding gene transfer into human HSCs, even as late as 2001, the art acknowledged that gene transfer into human hematopoietic stem cells was problematic (Hanazono et al., 2001). The claimed invention must be enabled at the time of filing. However, the priority date of this application is June 5, 2000. Thus, the instant specification must provide an enabling disclosure for the claimed invention as of this priority date.

The specification contemplates that transfecting the ES cells with a nucleic acid encoding an MEF2 and contacting the cells with a differentiating agent will be sufficient to direct the cells to differentiate *in vivo* or *in vitro* into the appropriate cell type and functionally integrate into the tissue into which they are implanted. However, the state of the art for *in vivo* differentiation of ES cells is undeveloped. While much work has been done to develop techniques for the directed differentiation of ES cells *in vitro* to produce desired cell types, little is known about the behavior of these cells *in vivo* or how they will interact with the local environment when implanted into adult tissues. Jackowski (1995) details the limitations and unpredictability associated with the transplantation of neural tissue.

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the wide variety of stem or progenitor cell types that could be used, and the unpredictability for producing cells suitable for therapeutic transplantation, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention to produce useful cell compositions.

At page 5, paragraph 4 of the response, Applicants argue that one skilled in the art would have been able to introduce a nucleic acid molecule into human hematopoietic stem cells based on the

teachings of Cheng et al. (1998). Applicants assert that Cheng et al. reports an optimized retroviral gene transfer protocol that is "clinically applicable" to gene transfer into human hematopoietic stem cells. Contrary to Applicants' suggestion, the retroviral gene transfer protocol described by Cheng et al. was limited to *in vitro* uses. Hanazono et al. (2001, cited on the PTO-892 of 11/28/03) acknowledges that Cheng et al. (1998) demonstrates the use of **murine stem cell virus** and that these vectors "have been shown to result in improved expression of transgenes compared to MoMLV vectors *in vivo* in mice, and *in vitro* in human primary hematopoietic cells" and that "[t]hese vectors are being examined *in vivo* in nonhuman primate models" (page 16, column 2, paragraph 1). Thus, contrary to Applicants' suggestion, protocols for using MSCV to transfect human hematopoietic stem cells *in vivo* was not taught by Cheng et al. The instant claims encompass *in vivo* transduction of human hematopoietic stem cells, in the context of therapeutic protocols. Applicants' arguments are not commensurate in scope with the scope of the claims.

At page 6, paragraph 2 of the response, Applicants assert that "as set forth in the specification," the skilled artisan would have been able to use electroporation to introduce a nucleic acid molecule into embryonic stem cells, including human embryonic stem cells. However, the specification does not teach an electroporation protocol that can be used to transfect human embryonic stem cells. On the contrary, the specification teaches using adenovirus transduction for the genetic modification of human ES cells (see Example 6). No results are provided for the adenovirus transduction experiments.

At page 6, paragraph 3 of the response, Applicants assert that Eiges et al. (2001) electroporated human ES cells and observed successful transfection. However, although very low levels of reporter gene activity were detected in cells transfected by electroporation, the reference also states that "human ES cells do not survive electroporation well" (page 515, column 1, paragraph 1). Applicants further point to Zwaka et al. (2003) for demonstrating that electroporation can be used to produce transfected human ES cells. Applicants point to the reference's teaching of a transfection rate of 5.6×10^{-5}. However, this

transfection rate was obtained by use of a unique electroporation protocol that was specially adapted for human ES cells. See Zwaka et al. at page 1, column 2, paragraph 2, where the reference describes numerous modifications that had to be made to develop an electroporation protocol for **human** ES cells and to achieve the transfection rate to which Applicants refer. Contrary to Applicants' statements, the reference clearly demonstrates that routine methods of transfection were not used for transfecting human ES cells. Since Zwaka et al. is post-filing art, the skilled artisan would not have had the benefit of the teachings of Zwaka et al. because the reference was published in February 2003, well after the filing date of the instant application.

At page 7, paragraph 2 of the response, Applicants assert that transient expression is useful in the claimed invention and that antibiotic selection can be used to prepare progenitor cells in which a large percentage or all of the cells are selected to contain the introduced MEF2-encoding nucleic acid molecule. However, antibiotic selection is an *in vitro* technique and thus would not address the issue of poor *in vivo* transfection. As discussed above, the instant claims encompass *in vivo* transduction of progenitor cells, in the context of therapeutic protocols. Thus, Applicants' arguments are not commensurate in scope with the scope of the claims. Antibiotic selection cannot be used *in vivo*. Applicants further assert that the specification discloses the selection of MEF2c-expressing P19 ES cells using a neomycin resistance gene and selection with geneticin. However, P19 cells are a mouse cell line and therefore could not be used for therapeutic transplantation, which is the only patentable utility asserted in the specification for the cell compositions produced by the claimed methods, nor are they subject to the transfection difficulties being argued here, which is exclusively a problem relating to the transfection of **human** ES cells.

At page 7, paragraph 3 of the response, Applicants assert that the claimed methods of differentiating progenitor cells do not require a particularly high efficiency of transfection of human or other progenitor cells. Applicants reiterate that transfection can be followed by antibiotic selection and that in combination with selection, low efficiency transfection of progenitor cells can be useful in the

invention. However, since the specification asserts that the utility of the claimed invention is for therapy, this low efficiency transfection must be sufficient to produce a useful cell composition, suitable for therapeutic transplantation. The specification does not show that low level transfection would be suitable for the differentiation protocol recited in the claims, nor does it show that cell compositions resulting from low level transfection would have the use asserted in the specification, which is for therapeutic transplantation. Furthermore, as discussed above, antibiotic selection cannot be used *in vivo* and the claims encompass *in vivo* transduction. Thus, Applicants arguments are not commensurate with the scope of the claims.

At page 7, paragraph 4 to page 8, paragraph 1 of the response, Applicants assert that it is "well known in the art that growth and differentiation factors are present *in vivo* in the diseased or injured tissue environment." Applicants point to Jackowski at the paragraph bridging pages 308-309 for teaching that certain factors with neurotrophic activities are known in the art and that peripheral nerve transection results in large quantities of NGF being produced. Contrary to Applicants suggestion, transection is an injury, not "an ongoing pathological process." The instant specification asserts that the utility for the claimed invention is to provide cell compositions useful for therapeutic transplantation to treat Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Alzheimer's disease and other forms of dementia, and multiple sclerosis (pages 1-3). These diseases involve ongoing pathological processes that affect the survival or function of endogenous neurons as well as transplanted neurons. Neither the specification nor the prior art provides evidence that the cell compositions produced by the claimed method will provide a therapeutic effect in these environments upon transplantation. Furthermore, neither the specification nor the prior art provides evidence that *in vivo* differentiation of progenitor cells residing *in vivo* can be used to provide a therapeutic effect in such disease environments. Moreover, Jackowski points out that membrane-associated or extracellular matrix-associated molecules

that **inhibit** the successful regeneration of adult mammalian CNS and PNS axons are present in the CNS and PNS (page 311, column 1, paragraph 2).

At page 8, paragraph 2 of the response, Applicants argue that McDonald et al. (1999) provides evidence that appropriate environmental cues can be present in diseased or injured tissue. Again, this reference is directed to transplantation in rats that have an injury, not "an ongoing pathological process." The instant specification asserts that the cell compositions produced are intended for transplantation to diseased animals having an ongoing pathological process, such as in Alzheimer's disease etc.

At page 8, paragraph 3 of the response, Applicants assert that Liu et al. demonstrates that embryonic stem cell-derived oligodendrocytes replace lost myelin in the injured adult CNS. This reference has already been addressed in the previous Office Action (page 5, paragraph 3 of the action mailed 6/16/04). As set forth in the previous Office Action this reference "describes the use of healthy rats that have an induced lesion. Such animals do not have the disadvantage of exhibiting an ongoing pathological process." As pointed out above, "the functional integration of donor cells remains a highly demanding task that requires a profound understanding and control of the biological properties of both donor cells and the host environment" (Rossi and Cattaneo, 2002, page 401, column 2, paragraph 2, last sentence).

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH

shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER